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Ganter, Michael T ; Alhashemi, Jamal A ; Al-Shabasy, Adel M ; Schmid, Ursina M ; Schott, Peter ; Shalabi, Sanaa A ; Badri, Ahmed M ; Hartnack, Sonja ; Hofer, Christoph K

Abstract: Septic shock is a serious medical condition. With increased concerns about invasive techniques, a number of non-invasive and semi-invasive devices measuring cardiac output (CO) have become commercially available. The aim of the present study was to determine the accuracy, precision and trending abilities of the FloTrac and the continuous pulmonary artery catheter thermodilution technique determining CO in septic shock patients. Consecutive septic shock patients were included in two centres and CO was measured every 4 h up to 48 h by FloTrac (APCO) and by pulmonary artery catheter (PAC) using the continuous (CCO) and intermittent (ICO) technique. Forty-seven septic shock patients with 326 matched sets of APCO, CCO and ICO data were available for analysis. Bland and Altman analysis revealed a mean bias ±2 SD of 0.0 ± 2.14 L min−1 for APCO–ICO (%error = 34.5 %) and 0.23 ± 2.55 L min−1 for CCO–ICO (%error = 40.4 %). Trend analysis showed a concordance of 85 and 81 % for APCO and CCO, respectively. In contrast to CCO, APCO was influenced by systemic vascular resistance and by mean arterial pressure. In septic shock patients, APCO measurements assessed by FloTrac but also the established CCO measurements using the PAC did not meet the currently accepted statistical criteria indicating acceptable clinical performance.

DOI: https://doi.org/10.1007/s10877-015-9672-0

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Michael T. Ganter, MD DEAA[§]; **Jamal A. Alhashemi**, MBBS, MSc, FCCM*; **Adel M. Al-Shabasy**, MD*; **Ursina M. Schmid**, MD[‡]; **Peter Schott**, MD[‡]; **Sanaa A. Shalabi**, BSc, RN*; **Ahmed M. Badri**, MBBS*; **Sonja Hartnack**, VMD°, **Christoph K. Hofer**, MD, DEAA[‡]

[§] Institute of Anaesthesiology and Pain Medicine, Kantonsspital Winterthur, Brauerstr. 15, 8401 Winterthur, Switzerland

* Department of Anaesthesia and Critical Care, King Abdulaziz University Jeddah, P.O. Box 80215, 21589 Jeddah, Saudi Arabia

° Section of Epidemiology, Vetsuisse Faculty, University of Zurich, Winterthurerstr. 270, 8057 Zurich, Switzerland

[‡] Institute of Anaesthesiology and Intensive Care Medicine, Triemli City Hospital Zurich, Birmensdorferstr. 497, 8063 Zurich, Switzerland

Corresponding author:

Christoph K. Hofer, MD; Professor of Anaesthesiology

Institute of Anaesthesiology and Intensive Care Medicine, Triemli City Hospital,

Birmensdorferstr. 497, 8063 Zurich, Switzerland.

Phone +41 44 466 2209; Fax: +41 44 466 2743

E-mail: christoph.hofer@triemli.stzh.ch

ABSTRACT

Purpose. Septic shock is a serious medical condition. With increased concerns about invasive techniques, a number of non-invasive and semi-invasive devices measuring cardiac output (CO) have become commercially available. The aim of the present study was to determine the accuracy, precision and trending abilities of the FloTrac and the continuous pulmonary artery catheter thermodilution technique determining CO in septic shock patients.

Methods. Consecutive septic shock patients were included in two centres and CO was measured every 4 hours up to 48 hours by FloTrac (APCO) and by pulmonary artery catheter (PAC) using the continuous (CCO) and intermittent (ICO) technique.

Results. Forty-seven septic shock patients with 326 matched sets of APCO, CCO and ICO data were available for analysis. Bland and Altman analysis revealed a mean bias ± 2SD of 0.0 ± 2.14 L min^{-1} for APCO-ICO (%error = 34.5%) and 0.23 ± 2.55 L min^{-1} for CCO-ICO (%error = 40.4%). Trend analysis showed a concordance of 85% and 81% for APCO and CCO, respectively. In contrast to CCO, APCO was influenced by systemic vascular resistance and by mean arterial pressure.

Conclusions. In septic shock patients, APCO measurements assessed by FloTrac but also the established CCO measurements using the PAC did not meet the currently accepted statistical criteria indicating acceptable clinical performance.

KEY WORDS

Sepsis; pulse wave analysis; thermodilution; pulmonary artery catheter; cardiac output, measurement; stroke volume, measurement.

INTRODUCTION

Severe sepsis and septic shock are serious medical conditions that still have a mortality of 20 to 30% despite contemporary critical care [1]. Early detection of sepsis as well as protocol-based and targeted treatment have been shown to be the key to success in reducing mortality in the last two decades [2-4]. Sepsis leads to organ dysfunction and failure, whereas the impaired tissue oxygenation plays a central role. Therefore, aggressive fluid and cardiovascular resuscitation is an essential part of the therapeutic bundles of the Surviving Sepsis Campaign with the goal of restoring organ perfusion and oxygenation early [5].

Haemodynamic monitoring is frequently used to guide and assess the response to fluid administration and cardiovascular drug support [6]. Traditionally, cardiac output (CO) has been measured invasively using the pulmonary artery catheter (PAC). With increased concerns about this invasive technique, a number of non-invasive and semi-invasive devices measuring CO have become commercially available [7]. Many of these devices are based on pulse wave analysis. Calibrated devices require external calibration to account for differences and changes in vascular tone between patients and within the same patient over time, respectively [8]. In contrast, un-calibrated CO devices such as the FloTrac (Edwards Lifesciences, Irvine, CA, USA) do not require external calibration [9]. Previous versions of FloTrac software have been extensively investigated and some studies revealed that the accuracy was somewhat disappointing in hyperdynamic and vasoplegic patients [10-12]. Therefore, the FloTrac software (third generation, G3) has been modified in order to better meet these needs [13]. However, the accuracy, precision and trending abilities in septic shock patients are still questionable [14-16].

The *first* aim of the present two-centre study was to determine the accuracy, precision and trending abilities of the G3 software of FloTrac assessing CO in septic shock patients. Since many clinicians use continuous CO (CCO) measurement by PAC to assess haemodynamics in this clinical setting, the *second* aim was to further report the performance of CCO in the same patient population. CO assessed by PAC intermittent thermodilution (ICO) served as reference method.

MATERIALS AND METHODS

This prospective, observational two-centre study was performed in the intensive care units (ICU) of a university and a university affiliated tertiary-care hospital with local Ethics Committee approval (Switzerland: Kantonale Ethikkommission Zurich, KEK Nr. STZ 20/90; Saudi Arabia: King Abdulaziz University Hospital Bioethics and Research Committee, Nr. 150-9) after written informed consent from the patients or their proxy. Patients were eligible for the study if they were at least 18 years old and admitted to the ICU with the diagnosis of septic shock (according to the criteria of the international sepsis definitions [17]). Patients were excluded from the study if they had a body weight <40kg, aortic or tricuspid regurgitation, cardiac arrhythmias (atrial fibrillation or flutter, and ventricular tachycardia), intra-aortic balloon pump treatment or any contraindication to the placement of a PAC.

Interventions and Measurements

In all patients the PAC (CCO VIP Pulmonary Artery Catheter, Model 139HF75P; Edwards Lifesciences, Irvine, CA, USA) was inserted through the internal jugular or subclavian vein and connected to a Vigilance monitor (Edwards Lifesciences, Irvine, CA, USA) that allowed CO assessment by intermittent (ICO) and continuous (CCO) thermodilution. A femoral or radial artery was cannulated and the arterial catheter was connected to the FloTrac transducer and attached to the Vigileo monitor with the G3 software release (Version 3.02; Edwards Lifesciences, Irvine, CA, USA) for continuous CO measurements derived from the arterial pressure waveform (APCO).

After set-up and study initiation, CO measurements were performed and repeated every 4 hours during a haemodynamic stable time period. ICO measurements were done using five 10 mL boluses of normal saline with a temperature < 10°C, randomly

injected throughout the respiratory cycle. Injectate temperature was measured at the injection site using a CO-set (Edwards Lifesciences, Irvine, CA, USA). For data analysis the mean value of at least 3 ICO measurements with a variability <15% were calculated. As a common, previously published procedure, single measurements were excluded from analysis in these sets of CO measurements if the variability was greater than 15% [18]. APCO and CCO data were recorded every minute and the quality of the APCO signal was checked every 4 hours by square wave test 5 min prior to ICO measurements. The APCO signal was considered adequate and consecutive measurements were allowed, if there was only one oscillation before returning to baseline after a snap flush to generate a square wave. APCO measurements were not done, if there were two or more oscillations before returning to baseline (underdamped curve) or if no oscillations were present (overdamped curve). 5 CCO values (two before and three values after ICO measurement over a 5-minute period) and 15 APCO values (7 values before and 8 values after ICO-measurement over a 5-minute period) were averaged. All hemodynamic data were automatically collected by a laptop computer connected to both the Vigilance and Vigileo monitors for a minimum of 24 hours.

FloTrac Algorithm

The proprietary FloTrac algorithm incorporates arterial blood pressure characteristics to assess CO using a multivariate model based on Otto Frank's model flow theory that has been described in detail elsewhere [19]. Briefly, the theory states that blood pressure fluctuates around the mean arterial pressure as a result of CO, i.e. stroke volume (SV) that is being pumped into the vascular system during each systole. Thus, the model has to adjust for cyclic changes of blood flow, pressure propagation

effects, vascular distensibility and peripheral resistance. To comply with these requirements the FloTrac algorithm works as follows:

1. Assessment of the contribution of pulse pressure on SV that is considered to be proportional to the standard deviation (SD) of arterial pulse pressure. The SD is correlated to stroke volume using an underlying database consisting of anthropomorphic and hemodynamic data that were collected using the thermodilution technique in a variety of patient populations and settings. Thus, for the set-up of the device the input if the patient's demographic data is required.

2. Integration of information about pulse pressure and vascular tone, primarily aortic compliance and different statistical moments of arterial pressure including skewness and kurtosis. Skewness and kurtosis describe arterial pressure wave symmetry and waveform distribution, respectively.

For the G3 algorithm update, the database was extended and more data of patients in septic shock conditions were included. Moreover, analysis of pulse wave characteristics was refined.

Statistical analysis

For statistical analysis Excel (Microsoft Office 2008 for Macintosh), IBM SPSS Statistics (Version 2.0, Release 20.0. IBM Corp, Armonk NY, USA) and Sigmaplot (Version 12.0, Systat, San Jose CA, USA) were used. Considering the concept of estimating total analytical error [20] the subsequently established guidelines recommend a minimum sample size of 120 paired samples [21]. Given the study duration of 48 hours with a minimum number of ICO measurements of 12 per patient and a 15% potential study protocol violation, a total of 45 patients were required in this study.

To describe the accuracy and agreement between intermittent CO (ICO) and the continuous CO measurement techniques (APCO, CCO), a modified Bland and Altman analysis adjusted for repeated measures was done [22, 23]. Thereby, bias ± 1.96 standard deviation (95% limits of agreement, LOA) was calculated using random effects models with R (version 3.1.1; packages “nlme” and “MethComp”), a software environment for statistical computing and graphics [24]. Different models were run containing additional variables to investigate the variability in measured CO values: systemic vascular resistance (SVR), mean arterial pressure (MAP), heart failure (HF, i.e. patients requiring inotropic support), CO measurements < 6 L min^{-1} vs. ≥ 6 L min^{-1} (CO6), the cannulation site (i.e. radial and femoral cannulation) as well as the two centres where the study has been performed. Percentage error (%error) was calculated according to Critchley and Critchley considering a threshold of 30% as indicator of a good clinical measurement performance [25]. To assess trending abilities of the continuous measurement techniques, concordance and polar plot analyses using half-circle polar plots were performed as recently suggested [26-28]. Central zone data (<0.5 L min^{-1}) representing statistical noise component were excluded from analysis. Trending ability was considered to be sufficient in clinical practice if (1.) concordance was ≥ 90-95% in the 4-quadrant plot and (2.) polar plot analysis showed an angular bias within ±5°, radial limits of agreement within ±30°, and polar concordance rate at 30° over 95%.

Test variability between the two centers was assessed using Student’s t-test. Unless otherwise stated, results are presented as mean±standard deviation (SD). A p-value < 0.05 was considered statistically significant

RESULTS

Patient characteristics

A total of 51 patients were enrolled in the study (Switzerland: n = 24; Saudi Arabia: n = 27), four patients had to be excluded because of severe aortic insufficiency (n = 2), severe intra-cardiac left-to-right ventricular shunt (n = 1) and dampened arterial pressure wave form (n = 1) that could not be resolved. Thus, data of 47 patients were available for analysis. Patient characteristics are depicted in ***Table 1***. Haemodynamic measurements were done during a time window of 39.8 ± 21.3 hours; mean time interval between subsequent intermittent CO measurements was 3.8 ± 2.2 hours.

Haemodynamics

326 matched sets of haemodynamic data were analysed in septic shock patients. Results are summarized in ***Table 2***. Data were observed over a wide range of haemodynamic conditions emphasized by the fact that SVR ranged from 282 to 2066 dyn sec^{-1} cm^{-5}. Moreover, in 44% of all haemodynamic measurements, CO was higher than 6 L min^{-1}, MAP was below 70 mmHg in 40% and SVR was below 800 dyn sec^{-1} cm^{-5} in 27%. CO changes ranged from -42% to +115%, -43% to +68% and -59% to +92% for ICO, APCO and CCO, respectively. All patients received vasoactive drug therapy support during the study period (norepinephrine n = 46, mean dose 22 ± 21 µg min^{-1}; vasopressin n = 22, mean dose 0.03 ± 0.01 U min^{-1}; dopamine n = 13, mean dose 537 ± 192 µg min^{-1}; ***Table 3***). A norepinephrine dosage of more than 30 µg min^{-1} was required in 21 patients (45%) and vasopressin in a maximal dosage of 0.04 U min^{-1} was given in 10 patients (21%).

Comparison of APCO and ICO

Bland and Altman analysis for APCO vs. ICO revealed an overall mean bias ± 1.96 SD of 0.00 ± 2.14 L min^{-1}; bias ranged from -0.01 to 0.63 L min^{-1} considering all subgroup analysis with limits of agreements between 1.74 to 2.48 L min^{-1} (***Figure 1***, ***Table 4***); overall %error was 34.5% and ranged from 30.5 to 35.9% for subgroup analysis. Random effect models didn't show any significant influence of low and high CO (cut off 6 L min^{-1}), heart failure with inotropic support and cannulation site (radial vs. femoral). However, these models revealed the bias between APCO and ICO measurements to be influenced by SVR and MAP: There was a significant effect of SVR on APCO-ICO ($p<0.0001$) and of MAP on APCO-ICO ($p=0.0007$).

Trend analysis for APCO vs. ICO revealed a concordance of 85% having excluded 157 of 326 data sets (exclusion zone = 0.5 L min^{-1}) with a significant correlation (r^2 = 0.504; p = 0.005). Using polar plot analysis an angular bias of 3 ± 35° was calculated with radial limits (95% CI) of -51 to +58°, Polar concordance at < 30° was 70% (162 of 326 data sets; exclusion zone 0.5 L min^{-1}; ***Figure 2***).

Comparison of CCO and ICO

Over all mean bias ± 1.96 SD for CCO vs. ICO was 0.23 ± 2.55 L min^{-1}, bias for subgroups was between 0.12 and 0.3 L min^{-1}, LOA between 1.61 and 3.84 L min^{-1} (***Figure 3, Table 5***). %error was 40.4% (overall) with a range between 33.1 and 45.6% (subgroups). Random effect model revealed no effect on bias between CCO and ICO measurements.

Concordance for trends was 81% (n=155, exclusion zone = 0.5 L min^{-1}; r^2 = 0.384; p = 0.005), angular bias was 0.1 ± 36° with radial limits (95% CI) of -57 to +57° and polar concordance < 30° was 71% (n=155, exclusion zone = 0.5 L min^{-1}; ***Figure 4***).

Comparison of performance between centres

Performance of CO assessment was comparable between the two centres: Variability between single bolus thermodilution measurements via PAC (ICO) was 8.3 ±12.4% in Switzerland and 7.7 ± 14.3% in Saudi Arabia (p = 0.09).

DISCUSSION

In this study on septic shock patients, CO measurements assessed by FloTrac (APCO) and by continuous pulmonary artery catheter thermodilution (CCO) did not meet the commonly quoted criteria for acceptability of agreement, i.e. the percentage error was greater than 30%. Random effect models revealed that APCO but not CCO was slightly influenced by low SVR and MAP, showing a tendency to underestimate CO in severe vasoplegia. Interestingly, the signal detection site, i.e. radial artery or femoral artery cannulation, did not influence APCO. Furthermore, trend analysis revealed slightly better performance for APCO but still both techniques, APCO and CCO did not meet criteria for acceptance. APCO and CCO cannot be used interchangeably.

In patients with septic shock the cardiovascular system is severely compromised. Large volumes of intravenous fluids and high vasoactive and inotropic drug support are required to maintain adequate blood pressure. However, the diagnostic and prognostic value of blood pressure is limited, since it does not reflect organ blood flow and thus oxygen delivery to the tissues. In a developing hemodynamic instability, low blood pressure is a late sign of impaired tissue perfusion, since blood pressure is typically maintained normal for a long time by increasing the sympathetic tone. Therefore, more sensitive, advanced hemodynamic monitoring that are capable of measuring global blood flow, i.e. CO is highly warranted to guide haemodynamics in this setting [29].

Despite the fact that the PAC use in clinical practice is declining [30], it is still the established standard method for CO estimation (ICO). Since its invasiveness and its lack to alter clinically relevant patient outcomes and costs, less invasive alternatives

are increasingly evolving. Nevertheless, they have to be validated against the clinical standard prior to routine use in critically ill patients [31]. Unfortunately, clinical validation is not without pitfalls. Critchley et al proposed that limits of agreement are acceptable up to a percentage error of ±30% between the standard CO (in the present study ICO) and the new CO measurement technique to be tested (here APCO and CCO) [25]. In the present study, APCO and even the widely used CCO technique showed a high percentage error, greater than 30% (34.5% and 40.4%, respectively). Thus, both techniques have to be considered unreliable. However, a recent meta-analysis showed that currently available CO devices often do not meet these strict criteria. The threshold has been questioned and the authors of the meta-analysis, Peyton et al, suggested that a percentage error of ±45% may be used and argued that this threshold represent a more realistic expectation of achievable precision [32]. Taken this definition, APCO and CCO would be considered adequately precise even in our severe vasoplegic septic patients.

In the present study, the reference technique showed a variability of roughly 8% for the repeated bolus measurements. Assuming an additional inherent measurement error of 11.6% observed by Yang et al [33] the total error accounts for 20% at best. This number is beyond the assumption that has been made for a percentage error threshold of 30%. However, more important than the ability of a device to reliably monitor absolute values is the capability to assess trends. In this study, APCO revealed an only moderate concordance and did not meet the proposed criteria of the polar plot analysis. It might be important to realize that in fact neither for the 4 quadrant plot nor the polar plot analysis (according to Critchley et al [26-28]) an adjustment for multiple measurement are being made, thus there is the possibility that a systematic error can influence results.

Three studies so far have validated the G3 software release of FloTrac in septic shock patients [14-16]. The present data are in accordance with the *first* study by De Backer et al where they could demonstrate an acceptable bias and a percentage error of 30% for APCO in 58 patients. Furthermore as in our results, APCO showed a tendency to underestimate ICO in severe vasoplegic patients [14]. The *second* study by Marqué et al reports a reduced accuracy in 18 patients and a percentage error being at 64%. They argued that their population consisted of patients suffering from even worse haemodynamic alterations requiring higher cardiovascular drug support [15]. Our patients however were comparable in terms of vasopressor and inotropes used. The main weakness of Marqué and colleagues study was rather that they compared APCO to CCO (not ICO). As shown in the present study, CCO by itself has its own inaccuracy and imprecision. It is therefore not surprising, that their reported bias and percentage error was much higher compared to the ones reported by our study and the study from de Backer et al. Finally, the accuracy of the FloTrac device in the *third* study performed by Slagt et al including 19 patients was somehow in between with bias ± 2SD of -0.2 ± 2.4 and percentage error of 53% [16].

The FloTrac in its previous versions was strongly influenced by SVR. Thereby, CO was significantly underestimated in patients with severe vasoplegia [10]. It has been postulated that the differences between central and peripheral arterial pulse pressures and the corresponding decrease in peripheral reflection of the pulse waves might be responsible for this phenomenon (decoupling of aortic and radial pulse pressure) [34]. Despite improved performance of the G3 software release of FloTrac our data show that there was still a tendency to underestimate CO in low SVR states and an influence of SVR on APCO. By contrast this could not be shown for CCO and one might argue that therefore CCO showed a better performance,

however, overall CCO revealed to have a high %error range (32-45%). Moreover, results of trend analysis for CCO showed number above the thresholds that are being used at the moment to define an acceptable device performance.

APCO and CCO are often considered as continuous and real-time measurement techniques. However, it has to be emphasized that this cannot be accepted as true. For both methods there is a so-called “response time”, i.e. a time window until a change of CO can be seen on the monitor. This time window is required in order to collect sufficient data to allow for acceptable measurements. In other words, a shorter sampling time will potentially increase an inherent measurement error but will enhance trending capabilities. Clearly, the advantage of APCO is the fact that sampling time was at 60 seconds during the study period and thus, this minimally invasive technique allows for almost real-time detection of CO changes. CCO (the Vigilance system) on the other hand is definitively not a real time technique with reported response times up to 10-12 minutes for the detection of 80-90% of CO changes [35, 36]. As a consequence the two techniques cannot be directly compared and cannot be used interchangeably in clinical practice.

The present study has some limitations. First, we compared APCO values from FloTrac to ICO determined by PAC, since there is no better reference method clinically available. CO determined by ICO measurement consists of an averaged set of bolus thermodilution values taken from the PAC with its own imprecisions [18]. Second, our patients with massive vasoplegia were treated with large doses of different vasopressors to maintain perfusion pressure. We have no data on the performance of APCO in untreated low SVR states and we cannot differentiate how the type of vasoactive or inotropic support affected APCO performance.

In summary, FloTrac APCO measurements did not meet the momentarily accepted statistical criteria in septic shock patients. Measurements seem to be influenced by SVR, i.e. vasoplegia and APCO had a tendency to underestimate CO assessed by bolus thermodilution. On the other hand, the established PAC CCO measurements did not meet the set criteria either, although measurements did not seem to be influenced by alterations of vascular tone. Despite the present findings, the FloTrac device may be considered as a first-line tool for patients in an early sepsis phase to guide haemodynamic management. More invasive CO devices and echocardiography may however be warranted in prolonged haemodynamic instability [37].

FUNDING

This study was supported by a grant of Edwards Lifesciences, Irvine, CA, USA.

CONFLICTS OF INTEREST, FINANCIAL RELATIONSHIP

In the past, CKH received lecturing fees and research grants from Edwards Lifesciences, Irvine, CA, USA. CKH has no other financial relationship with Edwards Lifesciences.

MTG, JAA, AMA, UMS, PS, SAS, AMB and SH have no conflict of interests to declare and have no financial relationship with Edwards Lifesciences.

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LEGEND FOR FIGURES

Figure 1

Title:

Bland and Altman analysis for cardiac output assessed by FloTrac (APCO) and intermittent thermodilution via pulmonary artery catheter (ICO).

Footnote:

A) Overall measurements: Solid line = bias and limits of agreement, dashed line = 95% Confidence Intervals (CI) for bias and limits of agreement.

B) Subgroup analysis (low vs. high cardiac output): Solid line = bias and limits of agreement for ICO < 6 L min^{-1}, dashed line = bias and limits of agreement for ICO ≥ 6 L min^{-1}.

C) Subgroup analysis (high vs. low systemic vascular resistance = SVR), solid line = bias and limits of agreement for SVR ≥ 800 sec^{-1} cm^{-5}, dashed line = bias and limits of agreement for SVR < 800 sec^{-1} cm^{-5}.

D) Subgroup analysis (cannulation sites), solid line = bias and limits of agreement for radial artery cannulation site, dashed line = bias and limits of agreement for femoral artery cannulation site.

All numbers are depicted in Table 4 in detail.

Figure 2

Title:

Trend analysis for changes in cardiac output assessed by FloTrac (APCO) and intermittent thermodilution via pulmonary artery catheter (ICO).

Footnote:

Four quadrant plot: Concordance = 85% (n = 165, exclusion zone = 0.5 L min^{-1}); solid line = regression line (r^2 = 0.504; p = 0.005). Semilunar polar plot: dashed lines: angular bias = 3±35° and radial limits (95% CI) = -51 to +58°; polar concordance at < 30° = 70% (n = 162; exclusion zone = 0.5 L min^{-1}).

Figure 3

Title:

Bland and Altman analysis for CO assessed by continuous (CCO) and intermittent (ICO) thermodilution via pulmonary artery catheter.

Footnote:

A) Overall measurements: Solid line = bias and limits of agreement, dashed line = 95% Confidence Intervals (CI) for bias and limits of agreement

B) Subgroup analysis (low vs. high cardiac output): Solid line = bias and limits of agreement for ICO < 6 L min^{-1}, dashed line = bias and limits of agreement for ICO ≥ 6 L min^{-1}.

C) Subgroup analysis (high vs. low systemic vascular resistance = SVR), solid line = bias and limits of agreement for SVR ≥ 800 sec^{-1} cm^{-5}, dashed line = bias and limits of agreement for SVR < 800 sec^{-1} cm^{-5}.

All numbers are depicted in Table 5 in detail.

Figure 4

Title:

Trend analysis for CO changes assessed by continuous (CCO) and intermittent (ICO) thermodilution via pulmonary artery catheter.

Footnote:

Four quadrant plot: Concordance = 81% (n = 155, exclusion zone = 0.5 L min^{-1}); solid line = regression line (r^2 = 0.384; p = 0.005). Semilunar polar plot: dashed lines: angular bias = 0.1±36° and radial limits (95% CI) = -57 to +57°; polar concordance at < 30° = 71% (n = 155; exclusion zone = 0.5 L min^{-1}).

Table 1: Patient characteristics

Sociodemographic		
F / M ratio	*n/n*	18 / 31
Age	years	61.4±16.9
Weight	kg	73.7±14.9
Height	cm	164.5±8.8
BSA	m^2	1.8±0.2
BMI	$kg\ m^{-2}$	27.2±4.5
History of disease		
CAD	*n (%)*	18 (37)
Heart failure	*n (%)*	13 (27)
DM II	*n (%)*	22 (45)
Hypertension	*n (%)*	19 (39)
Renal insufficiency	*n (%)*	16 (33)
Malignancy	*n (%)*	6 (12)
Other Systemic Disease	*n (%)*	28 (57)
Patient type		
Medical/Surgical ICU	*n/n*	31 / 18
Cause of septic shock		
Pneumonia	*n (%)*	21 (43)
Intraabdominal infection	*n (%)*	8 (16)
Urinary tract infection	*n (%)*	10 (20)
Other	*n (%)*	9 (18)

BMI = Body mass index, BSA = Body surface area, CAD = Coronary artery disease, DM = Diabetes mellitus, F/M = female / male

Table 2: Haemodynamic data during the study period

HR	beats min^{-1}	95±21	(40-167)
MAP	mmHg	73±10	(35-100)
ICO	L min^{-1}	6.0±2.3	(1.5-19.7)
ΔICO	L min^{-1}	-0.1±1.2	(-4.3-9.2)
APCO	L min^{-1}	6.2±1.8	(2.5-16.5)
ΔAPCO	L min^{-1}	-0.1±1.0	(-4.7-4.3)
CCO	L min^{-1}	6.4±2.3	(1.5-18.4)
ΔCCO	L min^{-1}	-0.1±1.4	(-11.7-3.6)
SVR	dyn sec^{-1} cm^{-5}	1017±336	(282-2066)

APCO = Cardiac output (CO) assessed by Flotrac, CCO = CO assessed by continuous thermodilution via pulmonary artery catheter, HR = Heart rate, ICO = CO assessed by intermittent thermodilution via pulmonary artery catheter, MAP = Mean arterial pressure, SVR = Systemic vascular resistance. ( ) = Range of observed values.

Table 3: Vasoactive and inotropic drug support during the study period

Norepinephrine	*n (%)*	46 (98.0)
	ug/min	22±21
Vasopressin	*n (%)*	22 (44.9)
	ug/min	0.03±0.01
Dopamine	*n (%)*	13 (27.1)
	ug/min	537±192
Dobutamine	*n (%)*	32 (65.3)
	ug/min	200±150
Milrinone	*n (%)*	6 (12.3)
	ug/min	570±260
Levosimendan	*n (%)*	0 (0)

Table 4: Bland and Altman analysis and percentage error for APCO versus ICO

	Mean bias (95%CI)	**lower LOA** (95%CI)	**upper LOA** (95%CI)	**%error** (*)
Overall	**0.00** (-0.24/0.24)	**-2.14** (-2.38/-1.90)	**2.14** (1.90/2.38)	**34.5** (25.5 - 44.5)
ICO <6 L/min	**0.27** (0.02/0.52)	**-1.48** (-1.73/-1.23)	**2.01** (1.76/2.26)	**35.8** (24.8 - 47.5)
ICO >6 L/min	-**0.41** (-0.81/-0.02)	**-2.88** (-3.28/-2.49)	**2.06** (1.66/2.45)	**32.3** (21.3 - 43.9)
MAP >70 mmHg	**0.10** (-0.21/0.40)	**-2.08** (-2.39/-1.77)	**2.28** (1.97/2.58)	**35.0** (24.0 - 47.1)
MAP <70 mmHg	-**0.16** (-0.44/0.13)	**-2.37** (-2.65/-2.09)	**2.06** (1.77/2.34)	**30.9** (25.4 - 47.6)
SVR >800 dyn/sec/cm^5	**0.27** (0.02/0.53)	**-1.65** (-1.91/-1.40)	**2.19** (1.94/2.45)	**35.9** (30.0 - 54.0)
SVR <800 dyn/sec/cm^5	-**0.63**(-1.03/-0.22)	**-3.11** (-3.51/-2.71)	**1.85** (1.45/2.26)	**30.5** (19.9 - 39.8)
No Heart failure	-**0.02** (-0.29/0.24)	**-2.22** (-2.49/-1.96)	**2.18** (1.91/2.44)	**34.6** (24.9 - 45.6)
Heart failure	-**0.01** (-0.51/0.50)	**-2.07** (-2.57/-1.56)	**2.05** (1.55/2.56)	**34.2** (19.7 - 53.1)
Radial cannulation	-**0.04** (-0.38/0.29)	**-2.11**(-2.44/-1.77)	**2.02** (1.69/2.36)	**34.6** (22.5 - 48.4)
Femoral cannulation	**0.04** (-0.31/0.38)	**-2.18** (-2.53/-1.84)	**2.26** (1.91/2.61)	**34.9** (22.9 - 48.3)

APCO = Cardiac output (CO) assessed by Flotrac; ICO = CO assessed by intermittent thermodilution via pulmonary artery catheter; LOA = limits of agreement; MAP = Mean arterial pressure, SVR = Systemic vascular resistance; %error = percentage error: * considering 95% CI of (APCO+ICO)/2 and LOA's

Table 5: Bland and Altman analysis and percentage error for CCO versus ICO

	Mean bias (95%CI)	**lower LOA** (95%CI)	**upper LOA** (95%CI)	**%error** (*)
Overall	**0.23** (0.00/0.46)	**-2.32** (-2.55/-2.09)	**2.78** (2.55/3.02)	**40.4** (31.5 - 50.3)
ICO <6 L/min	**0.25** (0.03/0.47)	**-1.36** (-1.58/-1.14)	**1.86** (1.64/2.08)	**33.1** (23.2 - 43.8)
ICO >6 L/min	**0.13** (-0.28/0.53)	**-3.20** (-3.61/-2.80)	**3.46** (3.05/3.86)	**42.2** (31.0 - 53.9)
MAP >70 mmHg	**0.24** (-0.04/0.51)	**-2.14** (-2.42/-1.86)	**2.61** (2.34/2.89)	**37.4** (27.4 - 48.9)
MAP <70 mmHg	**0.15** (-0.14/0.45)	**-2.61** (-2.91/-2.32)	**2.92** (2.62/3.21)	**44.1** (32.9 - 56.1)
SVR >800 dyn/sec/cm^5	**0.30** (0.08/0.52)	**-1.49** (-1.72/-1.27)	**2.09** (1.87/2.32)	**33.2** (16.2 - 28.8)
SVR <800 dyn/sec/cm^5	**0.12** (-0.33/0.57)	**-3.73** (-4.18/-3.27)	**3.96** (3.52/4.42)	**45.6** (53.5 - 91.3)
No Heart failure	**0.21** (-0.04/0.47)	**-2.30** (-2.56/-2.05)	**2.73** (2.47/2.98)	**38.5** (32.3 - 40.7)
Heart failure	**0.24** (-0.27/0.75)	**-2.49** (-3.01/-1.98)	**2.97** (2.46/3.48)	**45.1** (36.2 - 64.6)

CCO = CO assessed by continuous thermodilution via pulmonary artery catheter; ICO = CO assessed by intermittent thermodilution via pulmonary artery catheter; LOA = limits of agreement; MAP = Mean arterial pressure; SVR = Systemic vascular resistance; %error = percentage error: * considering 95% CI of (APCO+ICO)/2 and LOA's

Figure 1

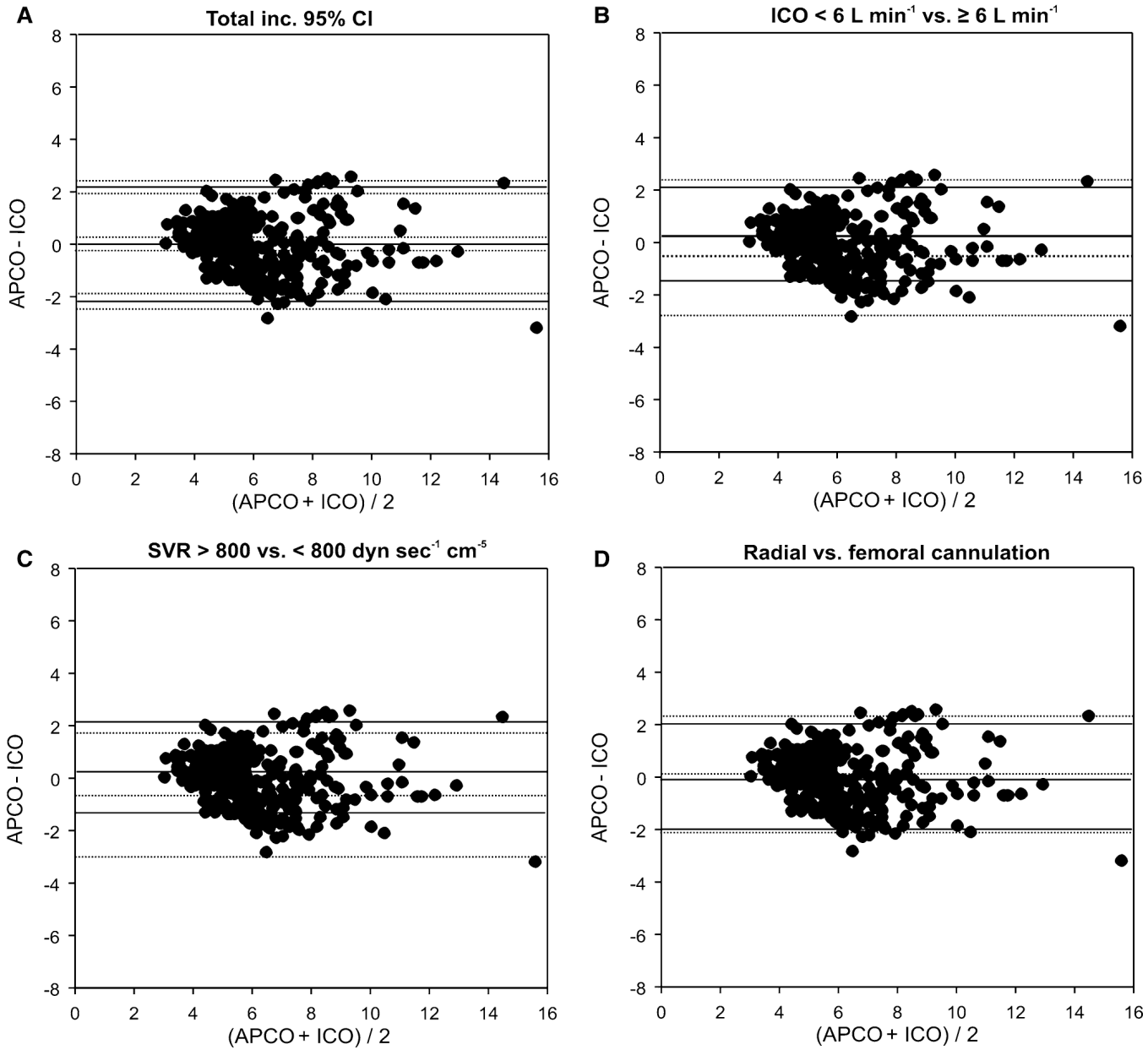

A
Total inc. 95% CI
B
ICO < 6 L min-1 vs. ≥ 6 L min-1
C
SVR > 800 vs. < 800 dyn sec-1 cm-5
D
Radial vs. femoral cannulation
APCO - ICO
(APCO + ICO) / 2

Figure 2.

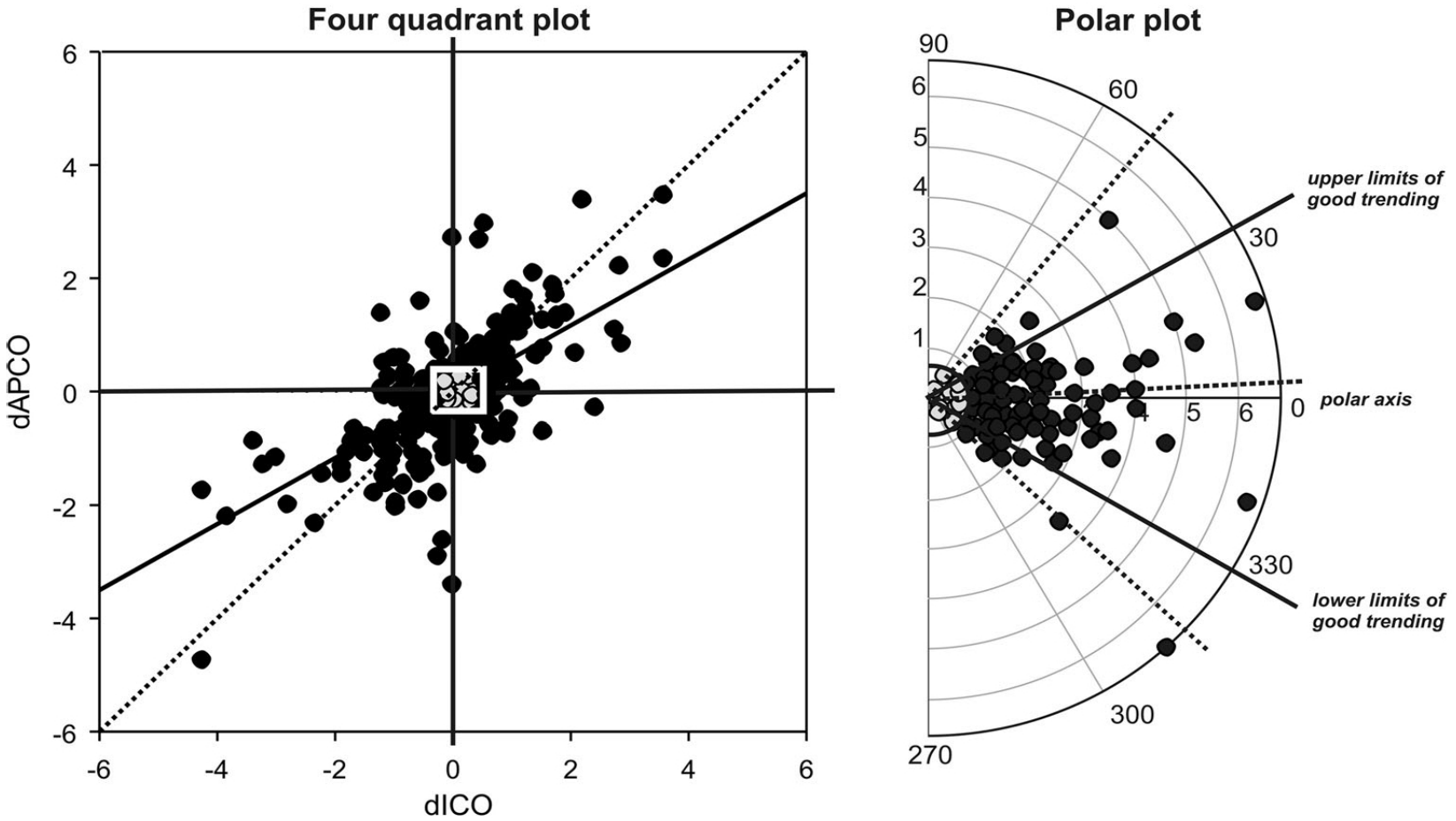

Four quadrant plot
dAPCO
dICO
6
4
2
0
-2
-4
-6
-6
-4
-2
0
2
4
6
Polar plot
90
60
30
0
330
300
270
1
2
3
4
5
6
upper limits of good trending
polar axis
lower limits of good trending

Figure 3.

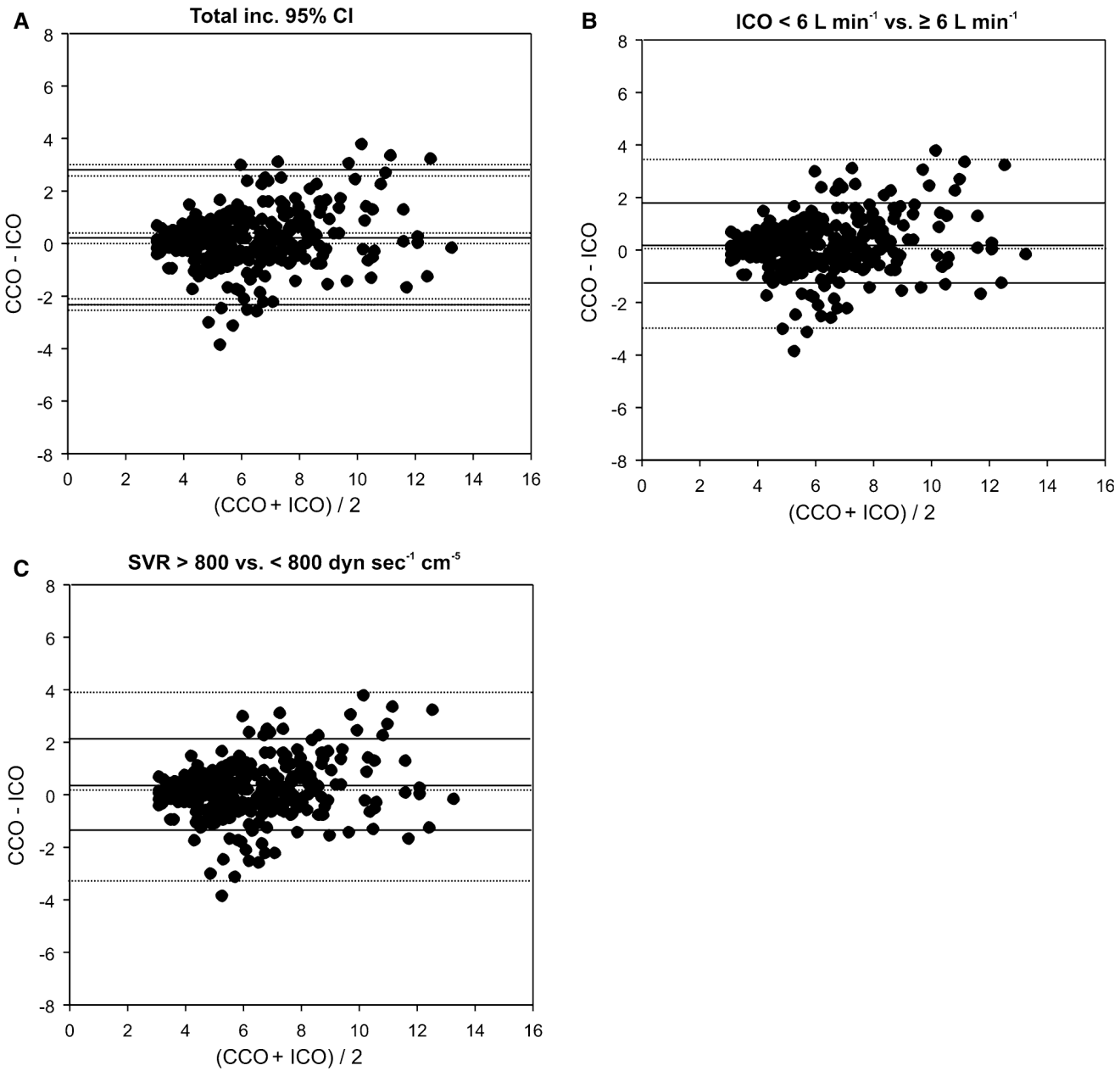
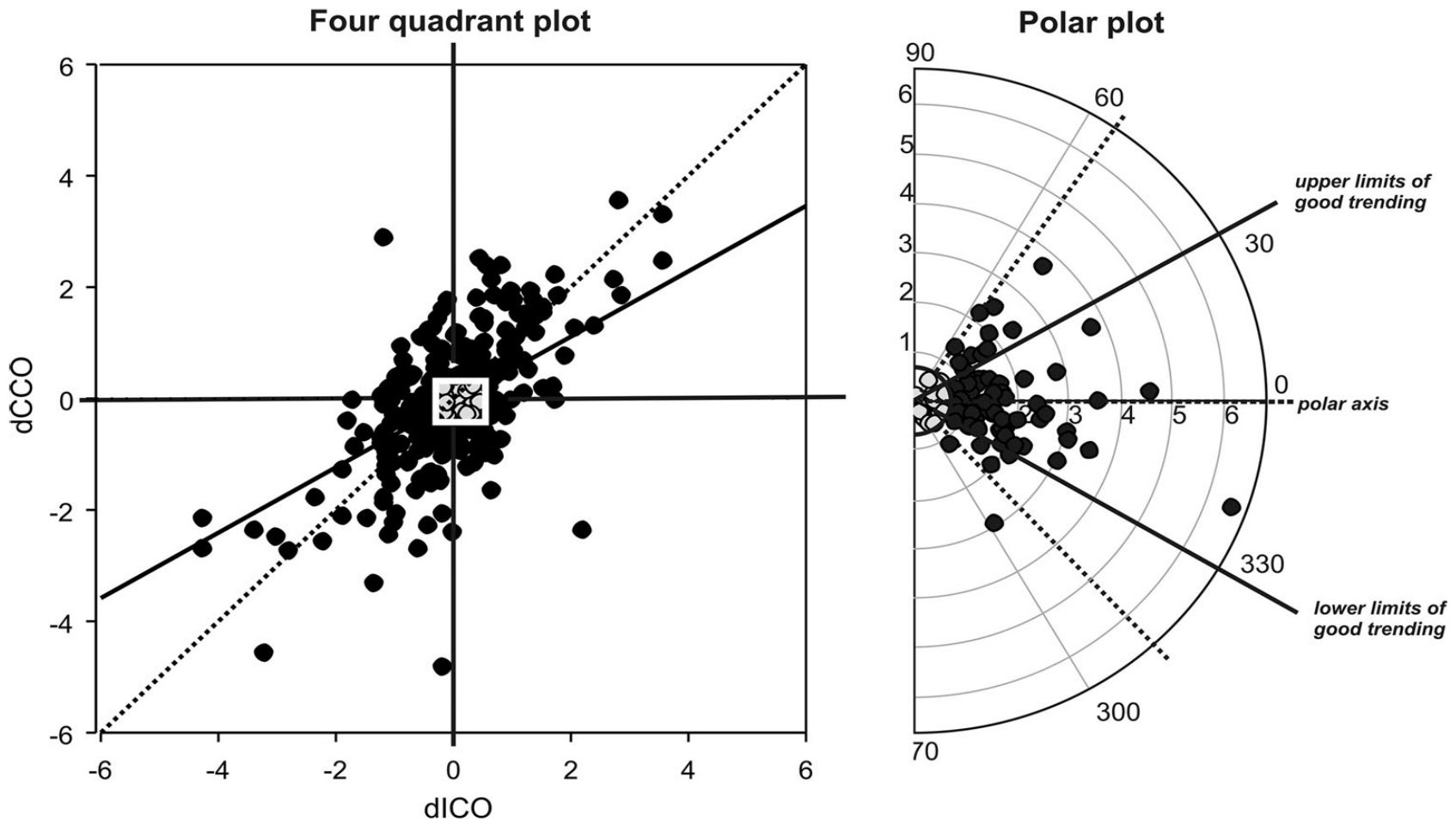

A
Total inc. 95% CI
CCO - ICO
(CCO + ICO) / 2
B
ICO < 6 L min-1 vs. ≥ 6 L min-1
CCO - ICO
(CCO + ICO) / 2
C
SVR > 800 vs. < 800 dyn sec-1 cm-5
CCO - ICO
(CCO + ICO) / 2

Figure 4.


Four quadrant plot
dCCO
dICO
6
4
2
0
-2
-4
-6
-6
-4
-2
0
2
4
6
Polar plot
90
60
30
0
330
300
70
1
2
3
4
5
6
upper limits of good trending
polar axis
lower limits of good trending